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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,623	06/27/2003	Haim D. Danenberg	4313-4005	7907
27123 7590 09/07/2007 MORGAN & FINNEGAN, L.L.P. 3 WORLD FINANCIAL CENTER NEW YORK, NY 10281-2101			EXAMINER JAGOE, DONNA A	
			ART UNIT	PAPER NUMBER
			1614	
			MAIL DATE	DELIVERY MODE
			09/07/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

**Application No.**

10/607,623

**Applicant(s)**

DANENBERG ET AL.

**Examiner**

Donna Jagoe

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 February 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-41 and 64-69 is/are pending in the application.
- 4a) Of the above claim(s) 2,3,10-15,18,21,22,27-30 and 66-69 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4-9,16,17,19,20,23-26,31-41,64 and 65 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

Applicants' arguments filed May 4, 2007 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

***Claims 1-41 and 64-69 are pending in this application. Claims 2, 3, 10-15, 18, 21, 22, 27-30 and 66-69 are withdrawn.***

#### ***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 6-9, 20 rejected under 35 U.S.C. 103(a) as being unpatentable over Hope et al. U.S. Patent No. 6,139,871 A.

Hope et al. teach encapsulated agents such as liposomes with an average diameter of 100 - 150 nanometers (0.1 - 0.15 microns) for treatment of atherosclerosis (see abstract). It does not teach the liposomes to treat a patient with an acute myocardial infarction. However, Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accidents (column 1, lines 17-24). It would have been

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made obvious to one of ordinary skill in art at the time it was made to infuse encapsulated agents such as liposomes in a size of 0.1 to 0.15 microns to treat atherosclerosis motivated by the teaching of Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction.

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-38, 40, 41, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ylitalo, Gen. Pharmacol. 2002 in view of Hope et al. U.S. Patent No. 6,139,871 A.

Ylitalo teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and teach that bisphosphonates inhibit atherosclerosis (page 287, column 1 to page 288, column 2). Ylitalo teaches that bisphosphonates anti-atherogenic effect is due to a direct effect on arterial wall wherein the bisphosphonates interact with the subendothelial lipid phagocytosing cells (page 292, column 1, paragraph 1) and macrophages are especially sensitive to bisphosphonates, and bisphosphonates suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis. Ylitalo does not teach depletion of macrophages, however, it teaches that the appearance of macrophages is suppressed. Since the term "depletion" is synonymous with the term "eliminating all macrophages", and both circumscribe methods of treatment having absolute success. Absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as atherosclerosis and AMI. Ylitalo does not teach treatment of a patient with AMI or reducing the zone of infarct following an AMI and it does not teach the size of the

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liposomes. However, Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). Hope et al. teach liposomes of 0.1 to 0.15 microns. It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI in a patient by administering encapsulated bisphosphonates in liposomes in a size of 0.1 to 1 micron motivated by the teaching of Ylitalo who teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and that bisphosphonates inhibit atherosclerosis and the teaching of Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction.

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64 and 65 are rejected under 35 U.S.C. 103(a) as being obvious over Golomb et al. U.S. Patent No. 6,719,998 B1. in view of Hope et al. U.S. Patent No. 6,139,871 A.

Golomb et al. teach treatment of restenosis (claim 1) and coronary restenosis (claim 5), by administering a liposomal bisphosphonate of 0.1 to 1.0 microns. One cannot treat restenosis unless stenosis or post angioplasty narrowing has occurred. Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI and reduce the zone of infarction by employing

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encapsulated agents such as liposomal bisphosphonates motivated by the teaching of Golomb et al. who teaches treatment of restenosis (claim 1) and coronary restenosis (claim 5), by administering a liposomal bisphosphonate of 0.1 to 1.0 microns and Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction.

Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64 and 65 are rejected under 35 U.S.C. 103(a) as being obvious over Golomb et al. U.S. Patent No. 6,984,400 B2. and Hope et al. U.S. Patent No. 6,139,871 A.

Golomb et al teach treating restenosis by administering a bisphosphonate in *inter alia* liposomes in sizes of from 0.01 to 1.0 microns (see claim 1). It teaches phagocytosis of bisphosphonate particles by inhibiting macrophages/monocytes (column 2, lines 23-65). It does not teach AMI. One cannot treat restenosis unless stenosis or post angioplasty narrowing has occurred. Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI with encapsulated agents such as liposomal bisphosphonates motivated by the teaching of Golomb et al. who teaches treatment of restenosis (claim 1) by administering a liposomal bisphosphonate of 0.1 to 1.0 microns and Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction.

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Claims 1, 4-9, 16, 17, 19, 20, 23-26, 31-41, 64 and 65 are rejected under 35 U.S.C. 103(a) as being obvious over Golomb et al. U.S. Patent No. 7,008,645 B2.

Golomb et al teach treating restenosis by administering encapsulated bisphosphonate) see abstract) such as liposomes (column 5, lines 43-44) in sizes of from 0.01 to 1 micron (column 9, lines 55-58). It teaches that bisphosphonates inactivate monocytes/macrophages (column 5, lines 4-7). It does not teach AMI. One cannot treat restenosis unless stenosis or post angioplasty narrowing has occurred. Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI with encapsulated agents such as liposomal bisphosphonates motivated by the teaching of Golomb et al. who teaches treatment of restenosis (abstract) by administering a liposomal bisphosphonate and Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction.

### ***Response to Arguments***

Applicant asserts that one skilled in the art would not apply the Hope reference for the treatment of AMI because the action of the formulations taught in Hope cannot directly treat AMI, even though they may be useful as a treatment for atherosclerosis. In response to applicant's argument that Hope et al. is nonanalogous art, it has been

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held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, it would have been made obvious to one of ordinary skill in art at the time it was made to infuse encapsulated agents such as liposomes in a size of 0.1 to 0.15 microns to treat atherosclerosis motivated by the teaching of Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction. It is noted that there is no agent recited in instant claims 1, 6-9 and 20. The claims are drawn to a method of treating a patient with an AMI comprising an encapsulated agent and Hope encompasses the size ranges of claims 6-9. Of further note is claim 20 drawn to a liposome, dependent on claim 1 wherein the active agent is not recited. Regarding the analogy for treatment of lung cancer by placing a nicotine patch on a patient's chest, it would not be outside the realm of possibilities to place a nicotine patch, although one would not employ the chest region because patches are generally placed on the upper extremities. If the lung cancer patient smokes, a skilled physician would employ means to cease the behavior that is the likely cause of the lung cancer in addition to employing means to treat the cancer. This would include employing means such as nicotine patches or gum. Regarding the atherosclerosis patient, the claim language comprising leaves the claim open for the inclusion of unspecified ingredients, even in major amounts, and as such, does not exclude the use of other lifesaving means. Hope et al. teach encapsulated agents such as liposomes with an average diameter of 100 - 150



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nanometers (0.1 - 0.15 microns) for treatment of atherosclerosis (see abstract) and restenosis of lesions in the coronary arteries (column 9, lines 1-3). Restenosis implies that stenosis or AMI has occurred.

Applicant asserts that neither Little nor Hope teach or suggest to the skilled artisan that their compositions or methods could be useful to treat the injury resulting from AMI and asserts that the treatments of Ylitalo and Hope are directed to treating and preventing atherosclerosis by preventing blockages in a blood vessel. Ylitalo et al. teach bisphosphonates encapsulated in liposomes interact with the subendothelial lipid phagocytosing cells (page 292, column 1, paragraph 1) and macrophages are especially sensitive to bisphosphonates, and bisphosphonates suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis. Hope et al. teach encapsulated agents such as liposomes with an average diameter of 100 - 150 nanometers (0.1 - 0.15 microns) for treatment of atherosclerosis (see abstract) and restenosis of lesions in the coronary arteries (column 9, lines 1-3). Restenosis implies that stenosis or AMI has occurred. Although the prior art does not recite reduction of the zone of infarct, Hope et al. teach that the encapsulated agents are useful for restenosis of lesions in the coronary arteries. One of ordinary skill in the art of cardiology would have found it obvious to update the prior art method of treating restenosis with the newer method of treatment of myocardial infarction and thereby gain, predictably, the commonly understood benefits of such an adaptation, that is, interaction with the subendothelial lipid phagocytosing cells (Ylitalo page 292, column 1, paragraph 1) and the disclosure that macrophages are especially

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sensitive to bisphosphonates, such that bisphosphonates suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis.

With regard to the Golomb et al. '998 reference in view of Hope et al., applicant asserts that Golomb et al. does not teach or suggest a method of treating an acute myocardial infarction or reducing the zone of infarct as claimed. In response, One of ordinary skill in the art of cardiology would have found it obvious to update the prior art method of treating restenosis with the newer method of treatment of myocardial infarction/zone of infarction and thereby gain, predictably, the commonly understood benefits of such an adaptation, that is, since the treatment for restenosis by administering a liposomal bisphosphonate of 0.1 to 1.0 microns is successful, one would have been motivated to employ the same compositions to treat a myocardial infarction and reduce the zone of infarct since the treatment was successful in restenosis.

With regard to the Golomb et al. '400 reference in view of Hope et al., applicant asserts that Golomb et al. does not teach or suggest a method of treating an acute myocardial infarction or reducing the zone of infarct as claimed. In response, One of ordinary skill in the art of cardiology would have found it obvious to update the prior art method of treating restenosis with the newer method of treatment of myocardial infarction/zone of infarction and thereby gain, predictably, the commonly understood benefits of such an adaptation, that is, since the treatment for restenosis by administering a bisphosphonate particulate is successful, one would have been

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motivated to employ the same compositions to treat a myocardial infarction and reduce the zone of infarct since the treatment was successful in restenosis.

With regard to the Golomb et al. '645 reference in view of Hope et al., applicant asserts that Golomb et al. does not teach or suggest a method of treating an acute myocardial infarction or reducing the zone of infarct as claimed. In response, One of ordinary skill in the art of cardiology would have found it obvious to update the prior art method of treating restenosis with the newer method of treatment of myocardial infarction/zone of infarction and thereby gain, predictably, the commonly understood benefits of such an adaptation, that is, since the treatment for restenosis by administering a bisphosphonate in formulations such as liposomes in sizes of from 0.01 to 1 micron and teaches that bisphosphonates are successful for inactivating monocytes/macrophages (column 5, lines 4-7), one would have been motivated to employ the same compositions to treat a myocardial infarction and reduce the zone of infarct since the treatment was successful in restenosis.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


### ***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 9:00 A.M. - 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Donna Jagoe  
Patent Examiner  
Art Unit 1614

August 29, 2007



ARDIN H. MARSCHEL  
SUPERVISORY PATENT EXAMINER